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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,224	03/02/2004	Yumi Matsuzaki	US-162	9934
38108	7590	01/27/2006	EXAMINER	
CERMAK & KENEALY LLP ACS LLC 515 EAST BRADDOCK ROAD SUITE B ALEXANDRIA, VA 22314			STEADMAN, DAVID J	
			ART UNIT	PAPER NUMBER
			1656	

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/790,224

Applicant(s)

MATSUZAKI ET AL.

Examiner

David J. Steadman

Art Unit

1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 November 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,5-7,9 and 10 is/are pending in the application.
- 4a) Of the above claim(s) 5-7 and 10 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 11/7/05.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Claims 1-3, 5-7, and 9-10 are pending in the application.
2. Applicant's amendment to the claims, filed on 11/4/2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.
3. Applicant's amendment to the specification, filed on 11/4/2005, is acknowledged.
4. Receipt of an information disclosure statement, filed on 11/7/2005, is acknowledged.
5. Applicant's arguments filed on 11/4/2005 in response to the Office action mailed on 8/11/2005 have been fully considered and are deemed to be persuasive to overcome some of the objections and/or rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.
6. The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

7. Claims 5-7 and 10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/13/2005.
8. Claims 1-3 and 9 are being examined on the merits.

Information Disclosure Statement

9. With the exception of the European Search report for EP 04004888.6 dated 7/23/2004, all references cited in the information disclosure statement (IDS) filed on March 18, 2005 have been considered in the prior Office action. The IDS filed on 11/7/2005 corrects a defect in the European Search report and this reference has been considered. A copy of Form PTO-1449 is attached to the instant Office action.

Claim Rejections - 35 USC § 112

10. Claims 2-3 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. It is unclear from claims 2-3 as to whether the recited modifications are meant to limit the modification in claim 1 that enhances glutamine synthetase activity or whether the recited modifications of claims 2-3 are separate and additional to the modification of claim 1. In the interest of advancing prosecution, claims 2-3 have been interpreted as being the modification in claim 1 that enhances glutamine synthetase activity. It is suggested that applicant clarify the meaning of the claim.

b. Claim 9 recites the limitation "the gene...encoding the arginine repressor." There is insufficient antecedent basis for this limitation in the claim. It is suggested that, for example, applicant replace "the" in "the gene" with "a."

Claim Rejections - 35 USC § 112, First Paragraph

11. The written description rejection of claims 1-3 and 9 under 35 U.S.C. § 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action (see ¶13 at pp. 6-9 of the 8/11/2005 Office action).

RESPONSE TO ARGUMENT: Applicant argues the examiner has applied the wrong standard for satisfying the requirements of 35 U.S.C. 112, first paragraph. Applicant argues that there is no requirement that every species encompassed by a recited genus be described, only that a skilled artisan has a reasonable expectation of success at arriving at other members of the genus based on the disclosure and prior art. Applicant argues that the amino acid sequence of glutamine synthetase is known in the prior art and its structure is not required to satisfy the written description requirements.

Applicant's argument is not found persuasive. The examiner maintains the position that the single disclosed species fails to represent the variation within the genus of claimed coryneform bacteria.

Claim 1 is drawn to a genus of coryneform bacteria having L-arginine or L-lysine-producing ability having *any* modification that results in enhanced glutamine synthetase activity and *any* modification so that an arginine repressor "does not function normally" wherein the arginine repressor comprises a protein that has at least 90% homologous (homologous is interpreted herein as meaning "identical") to SEQ ID NO:16. Claims 2-3 limit the bacterium to *comprising* a modification that results in adenylation of glutamine

synthetase being reduced or eliminated optionally wherein the modification *comprises* a mutation at Y405. It should be noted that, in view of the recitation of “comprises a modification” in claim 2 and “said modification comprises” in claim 3, claims 2-3 do not limit the modification to those that are specifically recited and have been interpreted as encompassing other unidentified modifications. Claim 9 limits the bacterium of claim 1 to having a disruption in a gene encoding an arginine repressor.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only two species of the claimed genus of coryneform bacteria, i.e., strain 2256 Δ argR Δ glnE, also referred to as strain FERM BP-08630 and strain 2256 Δ argR Δ e, also referred to as FERM BP-08631. Other than these two representative species, the specification fails to disclose any additional species of the claimed genus of coryneform bacteria, which, because the coryneform bacteria can

Art Unit: 1656

have *any* modification that results in enhanced glutamine synthetase activity and/or *any* modification so that an arginine repressor does not function normally, the genus encompasses widely variant species. However, the specification discloses only two modifications that result in enhanced glutamine synthetase activity, optionally wherein the modification is reduced or eliminated adenylation of glutamine synthetase, *i.e.*, knockout of the *glnE* gene of SEQ ID NO:17 encoding adenylyltransferase and mutation of the adenylation site of the glutamine synthetase of SEQ ID NO:20 at position 405. The specification discloses only a single modification so that an arginine repressor “does not function normally,” *i.e.*, knockout of the *argR* gene of SEQ ID NO:15.

Given the lack of description of a representative number of modified bacteria, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

12. The scope of enablement rejection of claims 1-3 and 9 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action (see ¶14 at pp. 9-12 of the 8/11/2005 Office action).

RESPONSE TO ARGUMENT: Applicant argues a skilled artisan can determine those arginine repressor polypeptides that are at least 90% homologous (homologous is interpreted herein as meaning “identical”) and do not function normally. According to applicant, a “normal function” for an arginine repressor is well-known and disabling protein activity requires less knowledge than enhancing activity.

Applicants' argument is not found persuasive. The examiner maintains the position that the specification fails to enable the full scope of claimed coryneform bacteria. The claims are so broad as to encompass coryneform bacteria having *any* modification that results in enhanced glutamine synthetase activity and/or *any* modification so that an arginine repressor does not function normally. In this case, the modifications are not limited to the glutamine synthetase or arginine repressor protein, but broadly encompass other modifications as exemplified in Reference Example 1 beginning at p. 27 of the specification, wherein the activity of a protein that adenylates glutamine synthetase is reduced. As such, the scope of modifications encompasses modifications to proteins that modulate the activity of a glutamine synthetase and/or an arginine repressor. It should be noted that while applicant argues that less knowledge is required to disable the function of the arginine repressor that is required to enhance activity, it should be noted that claims 1-3 do not require that the function of the arginine repressor be disabled, only that the protein does not "function normally," which also encompasses enhanced activity. In view of the broad scope of the claims, a significant amount of non-routine experimentation is required to make all modified coryneform bacteria as encompassed by the claims. In this case, the specification discloses only two modifications that result in enhanced glutamine synthetase activity, optionally wherein the modification is reduced or eliminated adenylation of glutamine synthetase, *i.e.*, knockout of the *glnE* gene of SEQ ID NO:17 encoding adenylyltransferase and mutation of the adenylation site of the glutamine synthetase of SEQ ID NO:20 at position 405. The specification discloses only a single modification so that an arginine

Art Unit: 1656

repressor does not function normally, *i.e.*, knockout of the *argR* gene of SEQ ID NO:15.

The specification discloses only two working examples of coryneform bacteria comprising these modifications, *i.e.*, strain 2256 Δ argR Δ glnE, also referred to as strain FERM BP-08630 and strain 2256 Δ argRAde, also referred to as FERM BP-08631. Other than these working examples, the specification fails to provide any additional *specific* guidance for modifying a coryneform bacterium with an expectation of obtaining a bacterium having the desired activity/utility. The effects of modifying a bacteria, particularly modifications to nucleic acids encoding L-amino acid biosynthetic pathway enzymes with an expectation of the bacteria maintaining the ability to produce a desired L-amino acid, is *highly* unpredictable as evidenced by Rhee et al. (cited in the 8/11/2005 Office action), Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991, p. 247), and Witkowski et al. (*Biochemistry* 38:11643-11650).

In view of the broad scope of the claims, the lack of guidance and working examples, the high level of unpredictability, and the amount of non-routine experimentation required, it is the examiner's position that undue experimentation is required for a skilled artisan to make the full scope of claimed bacteria.

Claim Rejections - 35 USC § 103

13. Claims 1-3 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suga et al. (EP 1154020; cited in the 3/18/2005 IDS) in view of Jakoby et al. (*FEMS Microbiol Lett* 173:303-310; cited in the 3/18/2005 IDS) and Nakayama et al. (US Patent 3,849,250). The claims are drawn to an isolated coryneform bacterium that

has L-arginine or L-lysine producing ability, is modified to enhance glutamine synthetase activity, and is modified so that an arginine repressor which is at least 90% identical to SEQ ID NO:16 does not function normally.

Suga et al. teaches an arginine repressor protein (SEQ ID NO:18), which appears to be identical to the arginine repressor of SEQ ID NO:16 disclosed herein. Suga further teaches a coryneform bacterium having a knock-out of the corresponding arginine repressor gene. Suga et al. teaches that the resulting coryneform strain produced a "markedly larger amount" of L-arginine (pp. 8-9). The nitrogen source in the medium used in the L-arginine production method of Suga et al. is ammonium sulfate (p. 8-9). Suga et al. do not teach modifying the disclosed coryneform bacterium having a knock-out of the arginine repressor gene to enhance glutamine synthetase activity.

Jakoby et al. teaches cloning of a *C. glutamicum* glutamine synthetase gene, construction of a mutant *C. glutamicum* strain with a deletion of the glutamine synthetase gene, and recombinant expression of wild-type and a Y405F mutant glutamine synthetase (p. 304). Jakoby et al. teaches that glutamine synthetase is a "central enzyme of nitrogen assimilation" (p. 305, left column, bottom) and that the activity of wild-type glutamine synthetase is significantly reduced in the presence of ammonium, while the activity of the Y405F mutant was not downregulated in the presence of ammonium (p. 306, left column, top).

Nakayama et al. teaches that a nitrogen source, e.g., ammonium sulfate, is required in the medium used for the biosynthetic production of L-arginine using a coryneform bacterium (column 1, lines 41-58).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Suga et al., Jakoby et al., and Nakayama et al. for the coryneform bacterium having a knock-out of the arginine repressor gene of Nakayama et al. further modified to overexpress the Y405F glutamine synthetase mutant of Jakoby et al. One of ordinary skill in the art would have been motivated to modify the coryneform bacterium having a knock-out of the arginine repressor gene of Nakayama et al. to overexpress the Y405F glutamine synthetase mutant of Jakoby et al. in order to maintain a high level of glutamine synthetase activity, which, according to Jakoby et al. is a central activity for nitrogen assimilation, in the presence of an ammonium nitrogen source, which, as acknowledged by Suga et al. and Nakayama et al., an ammonium nitrogen source is required for the biosynthetic production of L-arginine by coryneform bacteria. One would have a reasonable expectation of success for the coryneform bacterium having a knock-out of the arginine repressor gene of Nakayama et al. further modified to overexpress the Y405F glutamine synthetase mutant of Jakoby et al. because of the results of Suga et al. and Jakoby et al. Therefore, claims 1-3 and 9, drawn to an isolated coryneform bacterium as encompassed by the claims would have been obvious to one of ordinary skill in the art.

Conclusion

14. Status of the claims:

Claims 1-3, 5-7, and 9-10 are pending.

Claims 5-7 and 10 are withdrawn from consideration.


Claims 1-3 and 9 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Thurs, 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656